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Medicinal importance of *Ferula asafetida* oligo-gum resins against infective diseases

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Abstract
Ferula foetida oligo-gum resin containing phytochemicals with anti-viral properties. In order to investigate medicinal values of *ferula assa-foetida* a literature searches were performed through PubMed and PMC academic publications. It contains five sesquiterpene cumarines namely, conferone, badrakemin, feslol, isosamarcandin and samarcandin with anti-viral properties against Rhinovirus (HRV) and Influenza A H1N1. Farnesiferol C and Farnesiferol b are novel chemical scaffolds with HRV-2 inhibiting potential at low micromole and mode of inhibition action was prevention of rhinovirus adsorption (HRV-2) and/or uncoating of the capsid of virus. 5′S-hydroxyumbelliprenin and 8′-acetoxy-5′S-hydroxyumbelliprenin, methyl galbanate, galbanic acid, farnesiferol-C, farnesiferol-A, conferol showed greater potency against influenza A virus (H1N1) (IC_{50} 0.26-0.86 µg/mL) than amantadine. Several studies demonstrated that cytotoxic and antitumor activity of Galbanic acid. Additionally, exhibits anti-bacterial effects, anti–diabetic effects, anti- fungal, antiulcer genic effect and hypotensive effects. Asafoetida oligo-gum resin will be beneficial in anti-viral drug productions against disease forming viruses.

Keywords: Ferula foetida, anti-viral, oligo-gum, phytochemicals

Introduction
From the beginning of the 2020, attention of the health communities has been highly focused on the viral mitigation procedures and human immunity enhancement treatments again due to the pandemic situation of the viral infections (COVID-19). Meanwhile health community of the Asian countries are concerning to herbal based precautions against the viral infections. Hense identifying novel antiviral drugs is more important and natural products are an excellent source of these discoveries when concerning the Ayurveda medicine for viral disease, *Ferula foetida* play important role, regarding antiviral treatments. Phytochemistry of the oligo gum resins of this plant is more critical.

It is reported that the name ' Assa-foetida' derives from the Latin word meaning the' carrier of bad smell.' It is also true that *asafoetida* is very often referred to as the' Devil's dunk,' which indicates the degree of unpleasant organoleptic character it has. However, it is interesting to note that asafetida's other common name is' Food of God,' mainly due to health benefits and medicinal effects [1]. *Ferula foetida* is a perennial that grows by 1.5 m to around 2 m and requires dry or moist soil. For the medicinal as well as for culinary purposes, the dried latex (oleo gum resin) obtained by making deep incisions in the roots or rhizomes is preferred [2].

The flowering stems are 2,5-3 m tall and 10 m wide and hollow. These flowering stems have a number of schizogenic ducts that produce resinous gums in the cortex. The small, dirty yellow-colored flowers are produced in large compound umbels. This plant's fruits are oval, small, flat, reddish-brown in color and contain milky. Roots are thick, solid, and pulpy. The bad scent originates from the resin-like gum extracted from the stem and roots [3, 4]. The plant is commonly known as ‘hing’ in hindi, ‘hingu’ in Sanskrit, ‘perunkayam’ in Sinhala, ‘perungayam’ in Tamil and "Asafoetida "in English. (ENVIS Centre of medicinal plants).

Phyto chemistry of the Ferula foetida reveals that cumarines and sesquiterpenes cumarines have been identified as the main phytochemical compounds. A large number of sesquiterpene cumarines have been reported from the *asa-foetida* [5].

Ferula assa-foetida found to have a range of activities such as antioxidant, antiulcer, hepato protective, antimicrobial, antimicrobial, although some recent studies have shown that it has an antiviral activity that is active against influenza A (H1N1) virus [6]. In addition to the above-mentioned effects, the oligo gum of the *Ferula foetida* shows gut health potential as well.

The results of some studies demonstrate Asafin's potential for intestinal health; a 100% natural green formulation using *Ferula assa-foetida*-derived soluble dietary fibers (galactomannans), with improved stability, water solubility and reduced organoleptic properties. Asafin's important capacity to reduce the ulcer areas in the gastric wall and to prevent infiltration of edema and leucocytes infiltration in the submucosal layers [7].

If attention focused on overall pharmacological activities of the *Ferula foetida, boiling* water extracts of the oligo gum resins contained anti-diabetic activities by enhancing the insulin contents in the bodies of mice [8].

Antifungal activities of the *Ferula foetida* resin have investigated and it has proved that there is an ability to inhibit the activities of the *Aspergillus* parasites [9]. Further oligo gum extracts of the *foetida* plant showed anti-tumor effect [10] and Antiulcer genic effect [11].

Another study has revealed that aqueous extracts of the oligo-gum extracts of the *foetida* plant showed hypotensive effects by decreasing blood pressure from 11 mmHg to 5mmHg in a dose-dependent manner in the experiments designed using the mice *in vivo* conditions [12]. And chemo preventive capability has been demonstrated using oral doses of the oligo gum giving to the female mice *in vivo* conditions. It showed a decrease of tumor burden in each animal from 5.45 to 3.6(1.25%) and 2.3(2.5%), and decrease of tumor volume from 3.2 to 1.6 (1.25%) and 1.3cm^3 (2.5%) [13].

It depicts the chemical structures of sesquiterpene coumarins which have been documented to date. Sesquiterpene coumarins of *Ferula assa-foetida* include umbelliprenin, 5-hydroxyumbelliprenin, 8-hydroxyumbelliprenin, Tadshiferin, Asacoumarin A, 8-acetoxy-5-Shydroxyumbelliprenin, Asacoumarin B and the composition of this compounds were subsequently revised. The structure of this compound was later revised and its structure was discovered to be similar to that of galbanic acid, assa foetidin, Franesiferol A, Franesiferol B, Franesiferol C, Galbanic acid, Conferol, Gummosin, Assafoetidinol A and Assafoetidinol B [14 15].

In addition to the sesquiterpene cumarines, some sulfur containing compounds have been isolated from the oligo resin of the *Ferula foetida* plant. Three major sulfur constituents that have been found in Ferula assa-foetida include2-butyl 1-propenyl disulfide, 1-(superorder) propyl 1-propenyl disulfide and 2-butyl 3-(methylthio)-2-propenyl disulfide [16].

Taxonomical hierarchy

Kingdom	-	Plantae
Subkingdom	-	viridiplantae
Infra kingdom	-	streptophyte
Superdivision	-	embryophytes
Division	-	Tracheophyta
Subdivision	-	Spermatophyta
Class	-	Magnoliopsida
Superorder	-	Asteraceae
Order	-	Apiales
Family	-	Apeacaea
Genus	-	ferula
Species	-	ferula asafoetida

Intend of this review article is to investigate the phytochemical significances of the *ferula assa-foetida* as well as involvement in the antiviral tasks. Actually it is important to understand the anti-virtual mechanisms and chemistry behind the anti-viral mechanisms of the secondary metabolites contains in the oligo resins of the *ferula assa-foetida* plant. In addition to that investigation the antibacterial and antifungal actions of the actions of phytochemicals and essential oils of the *ferula assa-foetida* against the various disease forming bacteria species and fungal species also to be carried out.

Methodology

Literature searches were performed using the words "*ferula foetida*" or "assa foetida" or "Hing in PubMed and PMC Academic Search Complete. These words have also been typed into popular search engines, including Google and Google Scholar, to discover secondary details and items containing this herb available for purchase through the Internet. All material, regardless of source, was reviewed, and the review framework was developed to represent the information available. Chemical structures of the phyto-Chemicals were drawn using "MedChem designer" software.

Results and Discussion

Antiviral properties of the *Ferula foetida*

Antiviral action against HSV virus

Antiviral properties of the *Ferula foetida* will be highly forced in this study. Oligo gum resins of the *ferula assa-foetida* contains mainly five types of the sesquiterpene cumarines namely, Conferone, Badrakemin, Feslol, Isosamarcandin and Samarcandin. These compounds differ depending on the presence or absence of the hydroxyl group, the position of double bonds and the chiral center configuration. That means the main difference between these compounds due to the different sesquiterpene units [17].

Several Terpenoids and Coumarins have demonstrated anti-HSV effects and coumarins with sesquiterpene have been tested for HSV treatment before. Sesquiterpene coumarins Badrakemin acetate, Cellerin and Samarcandin diastereomer available in *Ferula assafoetida* gum resin act with antimicrobial, antiprotozoal and antiviral effects [18].

According to the studies from anti-viral study group, CPE (Cytopathic effect) inhibitory assays were performed with the gum resin of *asafoetida* as well as its isolated sesquiterpene umbelliferons Microlobidene (1), Farnesiferol C (2), Farnesiferol B (3) and Kellerin (4**).** (Figure 1) They were performed in HeLa cells with pleconaril-sensitive HRV-1A, -2, -14, and -16 in HeLa cells. Findings from CPE-inhibitory assays showed it has a dose-dependent antiviral activity against HRV-2 for asafetida gum resin.

The 50% inhibitory concentrations of Farnesiferol C and Farnesiferol B are 2.51 and 2.61 µM, respectively. It is worth demonstrating the mechanism of the antiviral process [19].

Capsid-binding compounds have previously been shown to inactivate viruses directly or to prevent rhinovirus adsorption and/or uncoating [20] However, mode of inhibition action was the prevention of the rhinovirus adsorption (HRV-2) and/or uncoating of the capsid by the Farnesiferol C which isolated from the assafoetida. pleconaril was used as the positive control of this experiment.

Farnesiferol C, Farnesiferol b are novel chemical scaffolds with HRV-2 inhibiting potential at the low micromolar range, although gum resin asafetida has been clearly applied in Dioscorides for the treatment of upper respiratory diseases [19].

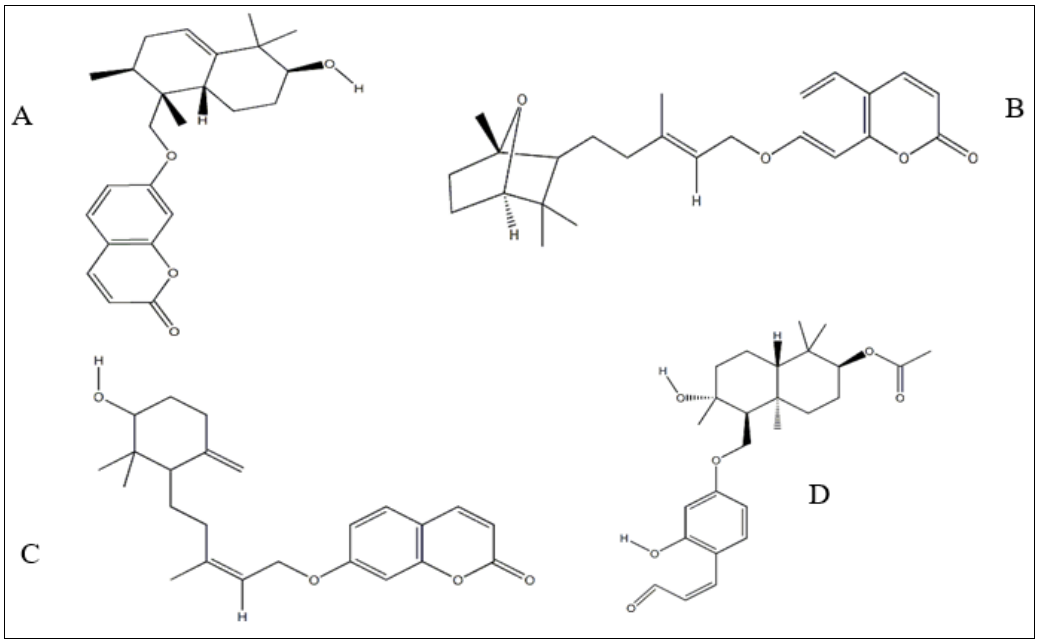

Fig 1: Sesquiterpene cumarines isolated from oligo-gum resin of *Ferula assa-foetida* showed anti-viral properties against Rhinovirus (HSV) A. Microlobidene, B. Farnesiferol c, C. Farnesiferol b, D. Kellerine

Antiviral action against Influenza A_H1N1 virus

Antiviral actions of the sesquiterpene coumarins, which isolated from the resin of the f. *assa-foetida* have demonstrated. Anti-influenza A Virus (H1N1) Bioassay has resulted positively against the virus. According to the IC_{50} value calculations of this experiment, 8′-acetoxy-5′S-hydroxyumbelliprenin, Methyl galbanate, Galbanic acid, Farnesiferol C, Farnesiferol A, Conferol (Figure 2) showed greater potency against influenza A virus (H1N1) (IC_{50} 0.26-0.86 µg/mL) than amantadine (IC_{50} 0.92 µg/mL), (positive control).

Among the isolated sesquiterpene cumarins from assa-foetida, the farnesiferol C (FC) has been investigated for their possible activity against the influenza A virus. It has been shown that all such compounds are more active than traditional antiviral compounds (Amantadine, IC_{50} 0.92 mg/ml) and indicated that FC may be an effective starting compound in the design and synthesis of a novel anti-H1N1 agent [21].

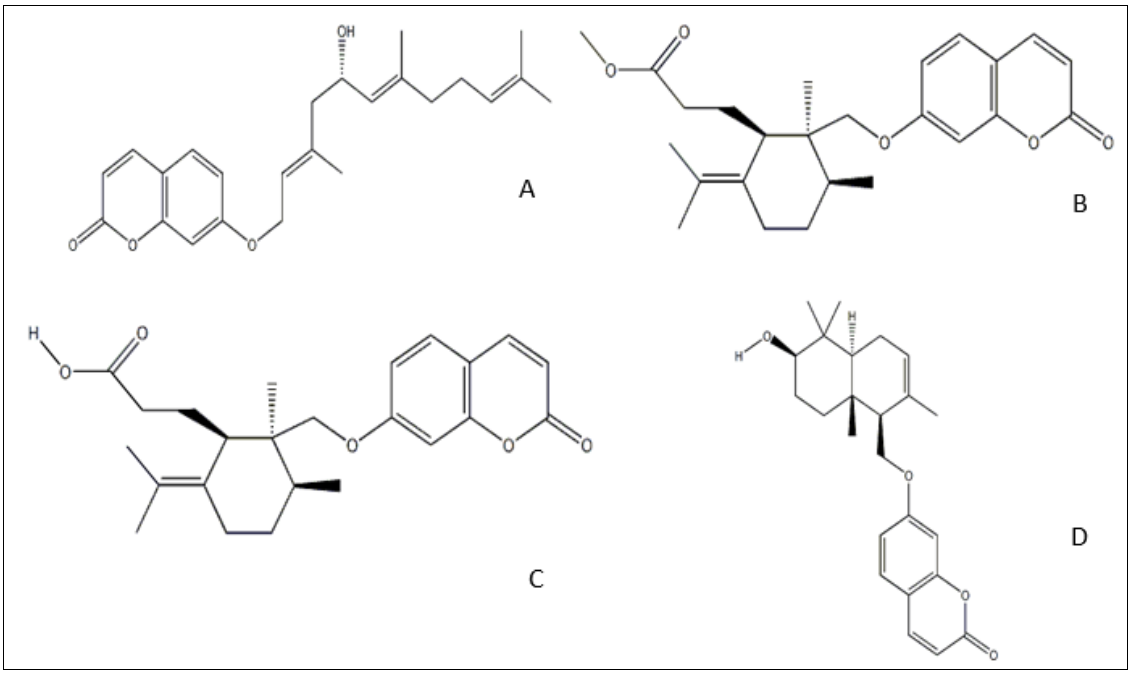

Fig 2: Sesquiterpene cumarines isolated from oligo-gum resin of *Ferula assa-foetida* against showed anti-viral properties against influenza A H1N1 virus. A. 8′-acetoxy-5′S-hydroxyumbelliprenin, B. Methyl galbanate, C. Galbanic acid, D. Conferol

Actions against Cytotoxicity

Several studies have been demonstrated that cytotoxic and antitumor activity of Galbanic acid (GA) which can isolate from the oligo-gum, a sesquiterpenoid coumarin, has recently been identified as an apoptotic and an agent of Geno / cytotoxicity, as well, GA interacts with DNA in partial intercalation mode through DNA groove binding and that van der Waals and electrostatic interactions form a complex [22]. There are different studies have been carried out to demonstrate the anti-tumor effect of the GA. A study has used GA loaded solid Nanoparticles (SLN) for effective anti-cancer treatment. According to the studies it verified that

SLNs could be used for sustainable delivery of lipophilic GA. Because GA is water-insoluble. So SLN makes more effective cytotoxicity of the GA by releasing slowly into the targeted tumor cells [23]. GA's cytotoxic and antitumor activity is linked to its anti-angiogenic and anti-proliferative properties that may occur through inhibition of human umbilical vein endothelial cell migration and P-glycoprotein inhibition as well [24].

Anti-bacterial and anti-fungal activities of the essential oils

Essential oils (EO) that can have identified in the *Ferula foetida* mainly as (E)-1-Propenyl sec-butyl disulfide (21.65%) 10-epi-γ-Eudesmol (19.21%) and (Z) 1-Propenyl sec-butyl disulfide (10.20%). **[25]** (Figure 3) (Z)-1-Propenyl sec-butyl disulfide as the third major component of the EO in our sample (10.20%) is the most common sulfur compound in the EOs of Ferula species, which plays an important role in the smell and taste of these plants in the smell and taste of these plants [26].

The EO has exhibited antibacterial activity against both methicillin-sensitive and resistant S. aureus in studies of this research. 0.5-4 µL / mL concentration range, and at a concentration of 2 µL / mL, EO of this plant successfully inhibited the growth of both normal and clinical isolates of S. *mutans* and S. *sanguis*. In addition, EO has demonstrated antibacterial activity against E. *faecalis* with MIC (Minimum Inhibitory Concentration) of 1 µL/mL. The EO displayed both bacteriostatic and bactericidal behavior against Gram-positive *B. cereus and L. monocytogenes* [27].

F. assa-foetida oleo-gum-resin with high (E)-1-Propenyl sec-butyl disulfide and 10-epi-γ-Eudesmol concentrations involved to inhibit the growth and killed all tested Candida strains at concentrations of 0.12-0.5 µL/mL [28]. Antifungal properties of *F. assa-foetida* EO against filamentous fungi such as Aspergillus species have reported previously [29]. In addition, above study the growth of examined dermatophyte clinical isolates such as *M. Gypsen, M. Canis, T. Rubrum* have been inhibited by *assafoetida* EO at 0.06-0.12 µL / mL and these pathogenic fungi were killed at concentrations ranging from 0.12 to 1 µL / mL [28].

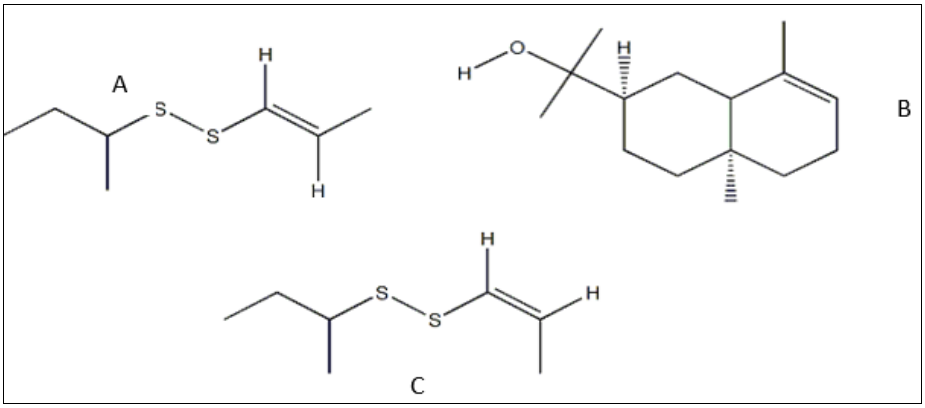

Fig 3: Main compounds in the essential oils (EO) of the *Ferula assa-foetida* A. (E)-1-Propenyl sec-butyl disulfide, B. 10-epi-γ-Eudesmol, C. (Z) 1-Propenyl sec-butyl disulfide.

Table 1: Summary of the anti- microbial actions of the sesquiterpene cumarins and essential oils isolated from oligo-gum resin of *Ferula assa-foetida*

Compound	Formula	Cas. No	Anti-microbial effect	Reference
Microlobidene	$C_{24}H_{30}O_4$	89782-66-4	Anti-viral effect against HSV virus	[19]
Farnesiferol C	$C_{24}H_{30}O_4$	512-17-4	Anti-viral effect against HSV virus	[19]
Farnesiferol B	$C_{24}H_{30}O_4$	54990-68-0	Anti-viral effect against HSV virus	[19]
Kellerin	$C_{26}H_{34}O_6$	54594-05-7	Anti-viral effect against HSV virus	[19]
8′-acetoxy-5′S-hydroxyumbelliprenin	$C_{26}H_{34}O_6$	154499-52-2	Anti-viral effect against influenza A (H1N1) virus	[21]
Methyl galbanate	$C_{25}H_{32}O_5$	1035947-90-0	Anti-viral effect against influenza A (H1N1) virus	[21]
Galbanic acid	$C_{24}H_{30}O_5$	3566-55-0	Anti-viral effect against influenza A (H1N1) virus	[21]
Conferol	$C_{16}H_{16}O_5$	1172120-53-4	Anti-viral effect against influenza A (H1N1) virus	[21]
Essential oil			Anti-bacterial effect against *Staphylococcus aureus,* clinical isolates of *S. mutans and S. sanguis,*Gram-positive *B. cereus and L. monocytogene*	[27]
Essential oil			Anti-fungal effect against Aspergillus species, dermatophyte clinical Isolates such as *M. Gypsen, M. Canis, T. Rubrum*	[29]
(E)-1-Propenyl sec-butyl disulfide	$C_7H_{14}S_2$		Anti-fungal effect against Candida strains	[28]
10-epi-γ-Eudesmol	$C_{15}H_{26}O$		Anti-fungal effect against Candida strains	[28]

Conclusion

Oligo-gum resins of the *F. assa-foetida* showed multi variate actions against disease forming microorganisms of Bacteria, Fungus, and Virus groups. Particularly different disease forming virus species. Anti-viral property of the oligo-gum resins mainly depends on the Phyto-Chemistry of the resin. Consequential research works have been carried out to investigate the anti-viral mechanisms against the critical disease forming viral species. Even, anti-viral effects of Oligo-gum resins' phyto chemicals have investigated only the limited group of virus species, resins of *F. assa-foetida* most probably can have an effect against most of the disease forming virus groups. And most of the studies reveals that some Sesquiterpene cumarines of the resin shows anti-viral activity against RNA viruses. So further investigation better to carryout to find anti-viral protection against Corona viruses such as COVID-19. Hence it can be proposed that more research should be focused on Oligo-gum resins of the *F. assa-foetida* to mitigating the viral pathogenic activities.

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